drugs characteristically produce headache, and they have a peripheral dilator mechanism. I feel that there is a component of hydralazine's action which involves histamine release, but of course it's so mixed that it's rather difficult to disentangle.

DR. SCHROEDER: I agree with Dr. Paton on that. As a matter of fact, when we give it to patients for the first time it looks as though the patients have got too much histamine in them and they even get a flu-like syndrome with pains in the back and stuffy nose and so on. Their rings get tight, they have edema without weight gain, their eyes are puffy, they flush, and many things happen that suggest histamine release. But to my knowledge, histamine is a vasoconstrictor, isn't it?

DR. PATON: That depends enormously on the person.

The Pharmacology of Ganglion Blocking Agents

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THE ACTIONS OF HEXAMETHONIUM AND PENTOLINIUM

It is hardly necessary to describe in detail the experiments on which our views of the action of drugs like hexamethonium and pentolinium are based. It is generally agreed that drugs of this type act simply by an ability to compete with acetylcholine at the cholinergic synapse of autonomic ganglia. They are themselves unable to excite the ganglion, but if the synapse is active, they reduce the efficiency of the transmission. Since the antagonism is competitive, the intensity of the block, i.e., the proportion of cells for which synaptic transmission fails, steadily increases as the concentration of hexamethonium or pentolinium in the extracellular space of the ganglion increases in relation to the acetylcholine released. This type of action can be extraordinarily selective. For practical purposes, ganglia only are affected and the response of peripheral effector organs to stimulants is unimpaired. Because these are quaternary salts, they must exist in solution as ions; that is, they have to carry about a positive charge with them, which greatly hinders their passage through cell walls. This gives them the other properties, not directly to do with ganglion block, of being excluded from the central nervous system, of being poorly absorbed by mouth, of reaching a concentration in the plasma such as is to be expected if they lead an extracellular life, and of being filtered by the kidney, neither being reabsorbed nor actively secreted. All this makes a tolerably coherent picture. The specificity found for these drugs in the laboratory has been fully justified in clinical practice; so much so, that no effect achieved by them should be interpreted in terms other than those of ganglion block. From time to time, peculiar reactions are observed and then additional properties are proposed, on the heart, on skeletal muscle or centrally; but if, on the one hand, one fully appreciates the pharmacologic evidence, and on the other, one views such reactions critically, I doubt that it is ever necessary to be driven to any other than ganglionic considerations, even when discussing such obscure problems as the pulmonary changes occasionally seen in treated malignant hypertension.[11]

THE PROPERTIES OF MECAMYLAMINE AND PEMPIDINE

The position is somewhat different when one turns to the newer ganglion blocking agents, of which mecamylamine and pempidine are of greatest interest at the moment. Mecamylamine is a secondary amine and pempidine a tertiary amine. They are alike in their dissociation constants and not widely dissimilar in molecular weights. The fact that they can exist, although only to a small degree, in the un-ionized form, transforms their characteristics.[1, 4, 6, 7, 9, 14, 19]

1. As is well known, they are active by mouth because they are, for practical purposes, completely absorbed. For accuracy's sake perhaps one should say that the absorption may not be strictly complete but certainly 50 per cent or better. This probably compares well with any other medicament given by mouth and means that, even if absorption varies, the proportion of the intended dose taken in cannot vary by more than a factor of two, and normally will vary much less.
2. At the same time, their fate in the body is much modified by their intracellular passage, for it is clear that many tissues, especially spleen, liver and lung and other tissues rich in nuclei, can take up mecamylamine and pempidine.
3. Thirdly, the renal handling of these compounds is changed. One might have wondered whether they would be treated like tetraethylammonium by being actively secreted by the tubules. It emerges, on the contrary, that the un-ionized form of these compounds is reabsorbed from the tubules. The rate of reabsorption, of course, depends on the amount un-ionized, hence the greater excretion when the urine is acid and the greater reabsorption when the urine is alkaline. This has offered the rather attractive idea of controlling duration of action by controlling the pH of the urine. However, other factors controlling duration of action, which do not depend on urinary pH, are also very important, so that the scope for control in this way is somewhat limited. The practical significance, perhaps, is rather that under conditions when the urinary pH may change, variations in apparent potency or in duration of action of these drugs must be anticipated.
4. Lastly, with mecamylamine and pempidine the possibility of central actions must be canvassed. There does not appear to have been much analytic work on this aspect, and indeed it would not be a very easy study. But it is sufficiently clear from the clinical reports that mecamylamine at least can have central effects leading to confusional states, tremor, mania and the like.

PROBLEM OF THE MECHANISM OF ACTION OF NONQUATERNARY GANGLION BLOCKING AGENTS

The differences between mecamylamine and pempidine, on the one hand, and hexamethonium and pentolinium, on the other, have been discussed so far as though they were purely pharmacodynamic. I suspect, myself, that this is true for practical purposes. But deeper differences of mechanism of action have been suggested, and the bases for this suggestion are worth examining.

1. Slowness of Action. One of the remarkable features of mecamylamine is that it has an action lasting many hours. Taking this with its known entry into and accumulation in cells,[14] the deduction that the latter causes the former is nearly irresistible. Further, if entry into cells is so important for time-course action, may it not also mean a different mechanism of action? Two comments must be made, however. The first is that for another group of drugs, the barbiturates, tissue take-up (in their case, by fat) is convincingly used to explain the *brevity* of action of drugs such as thiopentone, it being supposed that fat storage rapidly lowers plasma levels, and that the thiopentone, later slowly released from the stores, never reaches anesthetic levels in the plasma. I see no reason why a different situation should exist for mecamylamine. Indeed, the more a tissue concentrates mecamylamine, the lower will have to be the plasma level at which it is released again, and hence the less the chance that, during its release, effective plasma levels will be achieved. Of course, if mecamylamine produces a picture resembling ganglion block by combining intracellularly with nucleoprotein, then this tissue-concentration theory of prolonged action is eminently reasonable. But this one could not accept. The incidence of action by no means parallels distribution; spleen, kidney, lung and liver take up the most mecamylamine, up to 30 × plasma level; brain (as a sample of nervous tissue) only concentrates 8-fold. We can point, too, to substances concentrated in a similar way, but to a far greater extent, without significant ganglionic action, notably mepacrine. One could also remark that *any* drug active by mouth (and therefore able to penetrate cells) is liable to enter the tissues of the body; yet we do not attribute the extraordinary diversity of pharmacologic action among them to this single intracellular cause.

A second comment is that intracellular tissue binding is not *necessary* for prolonged action. We know of several quaternary salts, whose relative inactivity by mouth points to a failure of cell-entry, whose action is of comparable duration to that of mecamylamine—such as chlorisondamine, pentacynium (Presidal) and its relative 189c56, and compounds such as IN 391.[5, 12, 15] If, therefore, prolonged action can occur *without* intracellular binding, may not the association between the two be, for mecamylamine and pempidine, pure coincidence? Nor can we assume that compounds able to enter cells have necessarily prolonged actions, for some nonquaternary analogues of hexamethonium have similar durations of effect.[2]

At this point, perhaps, one ought to discuss what models for prolonged action the pharmacologist possesses. By conventional drug theory, one supposes that the onset and offset of action are dictated by two processes, the rate at which the drug combines (associates) with its receptors, and the rate at which it dissociates again. If the ratio between association and dissociation speeds is high, then the action of the drug is prolonged, since that amount combined takes a long time to get away; if the ratio is low, then the reverse. But there is another, less obvious prediction: If dissociation is relatively very slow, then the time taken to reach maximum action is also prolonged. Perhaps a domestic example may serve to illustrate this; suppose you turn on the taps (faucets) of a bath, and the drain-away is closed, then the bath will go on filling indefinitely. In other words, if dissociation doesn't occur at all, association will continue indefinitely (until limited by saturation). On the other hand, if the drain-away is both open and very large, equilibrium (with a virtually empty bath) is rapidly reached; here dissociation is rapid compared to association. Between these limits, the faster the rate of filling (association) of the bath (receptor area) compared to the rate of draining (dissociation), the longer it will take to reach any given approximation to the equilibrium state.

I have found this a generalization of rather wide application, when one studies, for instance, muscle relaxants, atropinic substances, antihistamines, and so on. For ganglion blocking agents, too, it seems enlightening. Take the series of drugs, TEA, hexamethonium, pentolinium, pempidine and mecamylamine, with durations of action ranging roughly from 30 minutes to 24 hours. As far as I can judge from the published data, the *shapes* of the time action curves are all alike, differing only in scale; and, roughly speaking, the time of maximum action is about one-sixth of the total duration. This is just what one would expect if the action of these drugs were dictated simply by the constants of association and dissociation. One may notice, too, that if, say, the difference in time course between mecamylamine and pentolinium makes one propose a different mode of action between the two, then the greater proportionate difference between pentolinium and TEA requires the same conclusion; and we multiply modes of action to an extent that one cannot accept.

One last point in this connection: If what I have argued is correct then, although there may be widely varying differences in time of peak effect, all the blocking agents should show some effect quite early. This indeed seems to be the case. There is no hint of any irreducible delay, with any of these agents, such as might point to the intervention, say, of a biochemical conversion, or to the poisoning of an enzyme to some critical level.

One may say, therefore, that the varying durations of action of ganglion blocking agents need point to nothing more than varying affinities for the receptor groups. But, surely, uptake into the tissues must influence time course somehow? My own guess is that this is true, but that the effect is different from that normally supposed; and that if you could prevent the tissue uptake (other factors remaining the same), duration of action and potency would be increased. At this point, it could be retorted that pempidine is taken up less than mecamylamine by the tissues, yet its duration of action is shorter, not longer. One can answer, besides referring to the long-acting quaternary agents, by another pharmacodynamic suggestion: It may well be that, among compounds able to penetrate cells, those that can do it best may also tend to be bound to the receptor area best. In that case, the association, with nonquaternary salts, of prolonged action and tissue take-up may be a coincidence of the type which might lead one to suggest, for instance, that poliomyelitis is caused by the internal combustion engine. The association between the latter rests, of course, on the common connection between them in civilized life. So, too, the prolonged action of a nonquaternary blocking agent and its tissue take-up may both flow, independently, from a special physiochemical property of the molecule.

2. Comparison of Clinical and Ganglion Blocking Potency. A second reason advanced for supposing mecamylamine to operate in a different manner from hexamethonium arises by comparing doses effective in man with those effective in blocking ganglia in animals. It is undoubtedly noticeable that whereas, say, mecamylamine and hexamethonium differ only slightly in potency as judged, say, by the dose required to produce 50 per cent block of a ganglionic response, the clinical dosage required per day (comparing parenteral hexamethonium with oral mecamylamine) is proportionately much higher for hexamethonium. But such a comparison is extraordinarily hazardous with agents of different durations of effect. Suppose that mecamylamine has an action eight times as long as hexamethonium. For comparable effects, hexamethonium would need to be given eight times as often; for a dosage of mecamylamine twice a day, this implies a dose of hexamethonium every one and one-half hours. Obviously, this will never be done; but a rather large and correspondingly wasteful dose of hexamethonium will be given less often. Under such circumstances, one can readily appreciate that the briefer acting drug will appear proportionately less effective.

In short, one suspects that while the laboratory investigation may compare intensities of block, clinical comparisons rest on the product of intensity with duration of action.

3. Differences in Type of Blocking Action on Ganglia. The very interesting statement has been made that the response of a ganglion partly blocked by mecamylamine does not fade with continued excitation at a fairly rapid rate (10 shocks/second) as it does with hexamethonium.[3] This could be a very important difference, both for mechanism, and for use, since, as will be argued later, the special sensitivity of a partly paralyzed ganglion to rapid or sustained excitation may be a valuable feature clinically. However, Corne and Edge[4] have not been able to demonstrate this difference, and my own experiments have failed to reveal it. I have no explanation for the divergence of my results from those of my esteemed collaborator, Professor Zaimis, and her colleagues. It is such things that make pharmacology interesting.

4. The Other Actions Possessed by Nonquaternary Ganglion Blocking Agents. A fourth reason for questioning whether the nonquaternary blocking agents act in the same way as hexamethonium arises from considering the effects on synapses or tissues other than ganglionic.[3, 4] It is clear that mecamylamine and pempidine can depress the heart beat (mecamylamine more than pempidine), and can depress the response of smooth muscle to the usual stimulants. Pempidine is reported to display, occasionally, a stimulant effect on the ileum and to have in large doses a pressor action, recalling, but not altogether similar in properties to, that seen with TEA. Mecamylamine has some vasodilator action on a dog's perfused leg.[4] But none of these effects seem likely to be significant in practice.

Two actions may, however, be more significant. First, neuromuscular effects. Both mecamylamine and pempidine can, in large doses, produce neuromuscular block. In smaller dosage, they potentiate d-tubocurarine and antagonize decamethonium and suxamethonium. Thus far, they are like the quaternary ganglion blocking agents. But Dr. Zaimis and her colleagues also describe an ability of mecamylamine to *change* the type of action of decamethonium and suxamethonium, so that the block they produce becomes, for instance, neostigmine-reversible.[3] One can, indeed, observe something of this sort sometimes with d-tubocurarine or hexamethonium, but less striking. There certainly is something fishy about mecamylamine; one's uncertainty arises from wondering how far its peculiarity depends on its prolonged action, which, as already stressed, makes it very hard to compare with briefer drugs. For our present purpose, the question is, What does this imply for the ganglionic synapse? Knowing what we now know of the extent to which ganglionic and neuromuscular actions can be dissociated, one must say that it *may* imply nothing; and it is in such a position of suspended opinion, waiting on further analysis, that perhaps the problem should be left.

The second action by mecamylamine, also reported by Dr. Zaimis and her colleagues, is that of a local anesthetic potency comparable with that of procaine; and, although it does not appear to have been explicitly tested, the same is doubtless true for pempidine. To interpret this, perhaps some work by J. W. Thompson and myself[17] on the synergism of procaine amide with hexamethonium is relevant, since procaine amide also possesses a local anesthetic action comparable with that of procaine, but it is far more stable. It has a fairly prolonged action on a ganglion, antagonizing both the action of acetylcholine, when it is released or injected, and the release itself by the nerve endings. When combined with hexamethonium, the block achieved is greater than purely additive, suggesting that to combine competitive block with a modest antagonism to acetylcholine release is one way of achieving a truly *potentiated* effect. In the light of such results, one wonders whether such a local anesthetic effect may not augment the ganglionic action of these nonquaternary amines. Certainly it could readily explain the rather modest reduction in acetylcholine output by a perfused ganglion seen for pempidine (in a large dose) by Corne and Edge[4] and for mecamylamine by myself. This reduction is certainly inadequate itself to cause block, but it might have some adjuvant influence. It is less certain whether, for a human dose, say of 1 mg./kg., this type of action is significant, for Thompson and I found that it needed more like 15 mg./kg. of procaine amide by the intravenous route to exert useful ganglionic effects. There is, however, something suggestive in all this, and it would be interesting to examine the behavior of other similar compounds with a rather greater local anesthetic activity.

5. Action on Acetylcholine Synthesis. The last suggestion to consider about the action of mecamylamine and pempidine is that they can interfere with acetylcholine synthesis. Although this could not explain their ability to antagonize, for instance, nicotine, it is a pertinent suggestion since any drug related to acetylcholine in one respect is liable to exhibit other relationships. Dr. J. E. Gardiner, in my laboratory, following his study of the hemicholiniums, has tested pempidine in this respect. He finds, however, that at concentrations of 10^{-4} and 10^{-3} molar, pempidine does not reduce acetylcholine synthesis by brain homogenates, nor by brain mitochondria (which contain the choline acetylase) whether the mitochondria are intact or broken. This means two things: pempidine does not interfere with the transport of choline into the cell or mitrochondrion, as the hemicholiniums do; nor does it block the intracellular choline acetylase.

6. Summary of Mechanism of Action. There is no decisive evidence that mecamylamine and pempidine block ganglia in any way different from hexamethonium, pentolinium or the long-acting quaternary salts. It is perhaps worth mentioning that although mecamylamine and pempidine are not quaternary, they are both such strong bases that over 99 per cent of the amount circulating or in tissue spaces will be in the ionized form, comparable with a quaternary salt. There is, however, a suspicion that some other factor *may* contribute, for which a feeble local anesthetic effect is a special candidate. Their prolonged action, like that of the long-acting quaternary compounds, can be attributed simply to receptor-affinity; and it is significant that the shape of the action-time curve is similar with all ganglion blocking agents, after making due correction for time scale.

THE POTENTIATION OF GANGLION BLOCK BY DIURETICS

Before leaving pharmacologic matters, mention should be made of the finding that two diuretics, acetazoleamide and chlorothiazide, can increase considerably the activity of ganglion blocking agents.[9, 10, 13, 14, 20] This promises to be a fairly straightforward story. First, both drugs tend to alkalize the urine, acetazoleamide the more strongly, in line with its stronger and more selective inhibition of carbonic anhydrase. Such alkalinization will, as mentioned earlier, increase reabsorption of the nonquaternary ganglion blocking amines; in fact, a delayed excretion under these conditions has been demonstrated. This type of potentiation, however, could affect only blocking agents which can exist in un-ionized form. The second feature is that both diuretics, but especially chlorothiazide, increase sodium output and diminish extracellular fluid. It was reported quite early in the clinical reports on ganglion block that low sodium diets sensitized to the blocking drug, and it seems reasonable to suppose that the same phenomenon is appearing in another form. One could envisage that sodium loss itself in some way brings this effect about, but it is more attractive and, so far, I think, permissible, to attribute it to the net loss of fluid, leading to a susceptibility to block comparable with that achieved, for instance, by a small hemorrhage. The only difficulty in this is the observation by Tapia *et al.*[20] that venous occlusion of three limbs, during the administration of chlorothiazide, does not have a significantly more pronounced effect than usual, as one might expect; but more work will no doubt clarify the position. The influence of sodium and water loss will, of course, extend also to quaternary blocking agents, and a potentiation of these, as well as of mecamylamine by chlorothiazide, has been described.

The possibility of sustained chlorothiazide administration, with the object of reducing the dose of ganglion blocking drug, immediately presents itself. This seems primarily a clinical problem in balancing advantages of dose on one side against dangers of electrolyte depletion, sensitization to the diuretic and the like, on the other. Perhaps one pharmacologist may be allowed to remark that, for his taste, despite a vested interest in drugs, the fewer that are used the better.

SOURCES OF VARIATION IN THE RESPONSE TO GANGLION BLOCK

Although there is no especially new work on the sources of variation in response to ganglion block, no discussion of the action of these drugs can be complete without some allusion to it, for it is one of the rather characteristic features of their use that patients require individual "titration" in assessment of their needs. There are three main ganglionic causes for such variation: the pattern of autonomic activity in an individual, the sensitization of ganglia by intense or prolonged excitation, and the varying susceptibility of different ganglia.

Ganglion block, like neuromuscular block, can reveal itself only if there is activity down an autonomic pathway. If a channel is inactive, the existence of block is only potential and not explicit. One would expect, therefore, that with the use of drugs one could even determine the autonomic activity normally present in the body by comparing the physiologic state of a man before and after block. This has some relevance to the notion that individuals can be classified as, for instance, vagotonic or sympatheticotonic. If this classification were true, one would expect to find individuals grouping themselves, after block, with either a selective parasympathetic or a selective sympathetic loss of function. This was a point that Dr. Steinberg and I took up in the practical pharmacology class at U.C.H. from 1951 to 1954.[18] In a group of students, one volunteer received 25 mg. hexamethonium bromide subcutaneously; the others subjected him to a systematic series of tests, before and after the drug, on supine and standing blood pressures and pulse rates, skin temperature, body temperature, salivary secretion, ocular accommodation of lens to distance and pupils to light, and of sweat rate. We then scored each subject as to whether a significant effect on various autonomic functions had been produced. The striking result was that no two subjects, in this fairly homogeneous population of over 40 healthy young students, gave the same pattern of response. It seemed, indeed, that there was no great division into two main groups, but that every subject possessed his own "autonomic fingerprint," as we termed it. In a way, this is obviously to be expected, for the autonomic carries the expression of our personalities, as well as a number of homoiostatic processes, and if personalities differ as they do, so should their bodily expression.

There is, however, another process which picks out active autonomic pathways; this is what can be termed an enhanced fatigability of the partly blocked synapse.[16] With a normal ganglion, increasing rates of excitation up to about 20/sec. yield increasing effector responses; this state of affairs is obviously a major requirement for the economy of the body, if autonomic reflexes are going to help in responding to, say, posture or hemorrhage. But after partial block, the ganglion becomes proportionately much more sensitive to the higher rates of excitation and to continued as opposed to brief excitation. The results of this are, first, that a short period of test stimulation may give a gross underestimate of the degree of block of sustained autonomic activity; secondly, that an acceleration of autonomic discharge rate, normally producing an increased response, may now produce a much smaller one, so that vigorous autonomic reflexes may be especially hard hit; and thirdly, that, among the various autonomic activities in the body, the most active will be picked out for deeper block, and the slower-paced ones may be less influenced. It is to this mechanism that one can turn to account for the persistence of postural hypotension, even when supine blood pressure is little different from normal, or for the extraordinary sensitivity to block of some patients, or for the resistance of some phasic autonomic reflex to block, when tonic responses are clearly reduced.

The third source of variation is that different ganglion cells, though exposed to the same concentration of blocking agent, may be blocked to varying degrees.[16] This observation is as old as J. N. Langley's experiments with nicotine, was repeated when Eccles studied ganglion action potentials, and has been repeatedly confirmed with later blocking agents. We have little certain explanation for it, although the known variations in ganglion cell structure and size and in preganglionic conduction velocities allow one to suppose that ganglionic synapses form a fairly widely distributed population with a significant variance in acetylcholine release, disposal and response. For the accessory ganglia, lodged in spinal nerves and rami communicantes, an inaccessibility to the drug may also be important.

One synapse may be mentioned here, that between the splanchnic nerve and the suprarenal medulla, which has the properties of an autonomic ganglion. Most investigators, including myself, have found that it is rather resistant to ganglion blocking agents, as tested by the pressor response to brief periods of repetitive stimulation. It is, however, a good deal more readily paralyzed when it is in a state of continued activity. This came out during some recent experiments on hemorrhagic shock, in which I used the method described by my colleague, J. R. Vane,[21] for testing the presence of sympathetic amines in blood. A suitable strip of isolated tissue (rat's fundus strip) is superfused with blood from an artery, the blood being returned by a vein; the preparation has considerable tone, and a small dose of Adrenalin or splanchnic nerve stimulation relaxes it. The method thus gives a continuous record of active substances in the blood. If now an animal is bled, the strip relaxes and stays relaxed as long as the hypotension persists, implying a sustained splanchnic-suprarenal activity. If now a dose of hexamethonium is given, the relaxation disappears promptly and completely, almost as though a tap supplying catechol amines had been turned off. Evidently, as with other synapses, tonic activity, especially of a vigorous kind, is more sensitive to block than phasic responses. No doubt, in the responses of patients to ganglion block, a temporary activation of the splanchnics, previously quiescent, would also break through, although a sustained activity would be paralyzed.

THE RELATION OF CHEMICAL STRUCTURE TO PHARMACOLOGIC ACTION

The connection of chemical structure with action is perhaps a topic that pharmacologists should discuss only among themselves. But the extraordinary properties of the methonium compounds and the more recent shock provided by mecamylamine have made this a subject of fairly general interest. I would like to describe briefly some recent work by E. W. Gill and H. R. Ing,[8] which has introduced some entirely new ideas. They seized on the odd fact that although hexamethonium blocks, the terminal groups it possesses are, alone, powerful ganglion stimulants. They pointed out that it seems only to be compounds with, so to speak, stimulant ends that are very sensitive to chain length. By contrast, bistriethylammonium derivatives change activity much less as the distance between the groups shortens or expands. Gill and Ing then formulated the hypothesis that, when hexamethonium acts, each end forms a union which would ordinarily excite the cell surface, that excitation normally involves some change in configuration of the surface, and that the reason hexamethonium does not excite is that this double combination "locks" the excitable surface so that the normal changes in permeability cannot take place; hence, hexamethonium paralyzes, despite the stimulant character of its terminal groups.

Gill and Ing have supported this with some new calculations, made possible by a recent advance in knowledge about the rotations of these chains, of the distance between the active groups, yielding a series of distribution curves of length against frequency. If they then suppose that activity depends on the proportion of molecules whose stimulant ends are between 4.8 and 6.0 Å apart, they are able to predict, in a really remarkable way, the ganglionic activity not only of the range of methonium compounds, but of many other series too.

Two other consequences follow. The first is, of course, that one could not assume that the receptors to which these compounds are attached are all spaced *exactly* the same distance apart; rather, one would expect a fairly narrow range of distances. If, then, one had an absolutely rigid molecule, even with its ends correctly distanced, it should be of low activity, because it can combine only with a small proportion of the receptor pairs. This, in fact, Gill and Ing verified. Thus, one needs, for this type of action, *some* flexibility in the molecule.

The second prediction tested by Gill and Ing was that by making a molecule partly rigid, partly flexible, they should be able to arrange that the majority of its possible configurations are within the relevant range. This too, they were able to establish.

The theory of Gill and Ing applies, of course, primarily to structures with two active groups. It supports the old, naive idea that Dr. Zaimis and I expressed in our original paper that the distance between the active groups was an estimate of inter-receptor distance on the ganglion cell membrane. But the significance of the work lies, I think, in the remarkable quantitative agreements which suggest that a real insight into the nature of the receptor membrane has been achieved. Although with structures like mecamylamine we move away from the compounds studied by Gill and Ing, I have no doubt that a physicochemical approach of comparable skill in other fields would prove equally rewarding.

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Pharmacology of Adrenergic Blockade in Hypertension

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Although the etiology of essential and malignant hypertension is still unknown, the importance of the sympathetic nervous system in maintaining the condition is generally accepted. Reports over the past years have shown a measurable degree of relief from surgical sympathectomy. The advent of potent adrenergic blocking agents a few years ago engendered the hope that these drugs might be useful in the treatment of hypertension by producing "chemical sympathectomy."

The use of members of the Fourneau series of adrenergic blocking agents in essential hypertension actually causes a rise in resting blood pressure. This effect of these compounds is undoubtedly due to a central stimulant action and unrelated to adrenergic blockade. Clinical treatment of hypertension with the more effective adrenergic blocking agents has also produced variable results, but favorable results have been obtained with the B-haloalkylamines in all degrees of hypertension.

It has been definitely established that vasomotor reflexes are still highly active in the presence of essential and malignant hypertension. The kidney is very responsive to vasoconstrictor impulses and to circulating norepinephrine. Inhibition of sympathetic vasoconstrictor tone by high spinal anesthesia has been shown to produce an increase in renal blood flow in both human essential hypertension and experimental hypertension in dogs. Phenoxybenzamine (Dibenzyline) is highly effective in preventing reflex renal vasoconstriction and renal vasoconstriction from epinephrine or norepinephrine. This can readily be demonstrated by injecting Dibenzyline into one renal artery of a dog and infusing ephinephrine or norepinephrine intravenously or by causing reflex vasoconstriction by bleeding. Any of these procedures will cause vasoconstriction and a reduction of renal blood flow on the uninjected side, while the renal blood continues at approximately the control rate in the kidney with adrenergic blockade. The role of renal vasoconstriction, if any, in the development and maintenance of essential and malignant hypertension has not been determined. Adrenergic blocking agents are, however, able to prevent renal vasoconstriction most effectively. Actually, the primary effect of adrenergic blockade in reducing the blood pressure in hypertension is by preventing the compensatory vasoconstriction that occurs on assuming the upright position.

The use of adrenergic blocking agents in the treatment of hypertension has been disappointing because of the numerous side effects. Particularly annoying are dizziness due to reduced cerebral blood flow and tachycardia on assuming the upright position.

Development of tolerance to the hypotensive action of adrenergic blocking agents is a characteristic finding. This is analogous to the gradual rise in blood pressure seen after surgical sympathectomy.

Discussion

JOSEPH R. DIPALMA, *Moderator*

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DR. DIPALMA: There are certain interesting problems concerning the pharmacologic activity of the last group of drugs that we've discussed. One is the problem of just how the blood pressure is lowered with ganglionic blocking agents. Is this, Dr. Paton, primarily due to a reduction in cardiac